(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

C6 cont'd

(b) receiving a plurality of biological pathway responses, each of said plurality of biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said plurality of biological pathway responses comprising biological pathway responses sufficient to cover all pathways likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said plurality of biological pathway responses, wherein each of said plurality of biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents said measured drug response data of said drug in said cell type.

REMARKS

The specification has been amended to correct a typographical error. No new matter has been added. A marked version of the paragraph in the specification which has been amended, with the amendments indicated by bracketing for deletions and underlining for additions, is attached hereto as Exhibit A. A clean version of the paragraph in the specification, as amended, is attached hereto as Exhibit B.

Claims 41-45 and 48-87 are pending in the application. In the instant Amendment, claims 41, 49, 80-83 and 85-87 have been amended and new claim 88 has been added to more particularly point out and distinctly claim the present invention. Upon entry of the above-made amendments, claims 41-45 and 48-88 will be pending. A marked version showing

changes made to the amended claims is attached hereto as Exhibit C. A clean version of the pending claims, as amended, is attached hereto as Exhibit D.

Claims 41, 80-83 and 85-87 have been amended to more particularly point out that in the computer systems of the invention, the one or more biological pathway responses that are combined to form, e.g., a model drug response, *comprise at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in the cell type* (emphasis added). Support for the amendments is found in the specification at, e.g., page 29, lines 3-19; and page 37, line 32 through page 38, line 8. Claims 41, 80-83 and 86-87 have also been amended to replace the term "identifying biological pathways" with the term "determining biological pathways." Support for the amendments is found in the specification at, e.g., page 29, lines 30-33.

Claim 81 has also been amended to more particularly point out that *the second drug is different from the first drug and exhibits therapeutic efficacy for the same disease or disorder as the first drug* (emphasis added). Support for the amendment is found in the specification at, e.g., page 9, lines 13-15. Claim 82 has also been amended to more particularly point out that *the second drug is different from the first drug and exhibits therapeutic efficacy for the same disease or disorder as the first drug* (emphasis added). Support for the amendment is found in the specification at, e.g., page 9, lines 28-30. Claims 81-82 have also been amended to correct typographical errors.

Claim 49 has been amended to more particularly point out that the claimed method involves randomizing the drug response with respect to the plurality of levels of drug exposure *or* randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways (emphasis added). Support for the amendment is found in the specification at, e.g., page 49, line 23 through page 50, line 9. Claim 49 has also been amended to incorporate the original step (iii) into step (ii). Claim 85 has also been amended to more particularly point out the invention.

New claim 88 has been added to more particularly point out the claimed invention. Support for the new claim is found in the specification at, e.g., page 29, lines 3-14; and page 37, line 22 through page 48, line 15.

No new matter has been added. Entry of the foregoing amendments and consideration of the following remarks are respectfully requested.

CORRECTION OF DRAWINGS

The Examiner has indicated that Applicant is required to submit drawing corrections within the time period set for responding to the Office Action. Applicants submit herewith formal drawings consisting of 12 sheets of drawings corresponding to Figures 1-9.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

Claims 49 and 85 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention. The Examiner contends that the claims are interpreted as a randomization of both drug response data as well as biological pathway response data, which is not supported in the specification. At the outset, Applicants respectfully point out that, contrary to the Examiner's contention, claim 85 recites in step (a) randomizing the drug response with respect to the plurality of levels of drug exposure, *or*, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways (emphasis added). As acknowledged by the Examiner, this is fully supported by the specification. Applicants have amended claim 49 to be consistent with the recitation in claim 85 such that the claim recites in step (i) randomizing the drug response with respect to the plurality of levels of drug exposure *or* randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways (emphasis added). Thus, claim 49 is also fully supported by the specification. The rejections of claims 49 and 85 under 35 U.S.C. § 112, first paragraph, should therefore be withdrawn.

Claim 45 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that the "Levenberg-Marquandt method" has not been set forth or referenced in the instant specification. At the outset, Applicants respectfully direct the Examiner's attention to the specification at page 46, lines 11-28 for a description and citation of a reference of the Levenberg-Marquandt method. The Examiner's contention is thus erroneous. Additionally, Applicants respectfully submit that the Levenberg-Marquandt

method is a well-known method for performing minimization. Anyone skilled in the art will be able to perform the minimization as claimed, using the Levenberg-Marquandt method based on the teachings in the specification and knowledge common in the art. Therefore, Applicants respectfully submit that the rejection over claim 45 under 35 U.S.C. § 112, first paragraph, is in error, and should be withdrawn.

Claims 41-45, 48-56 and 58-87 are rejected under 35 U.S.C. § 112, first paragraph, as lacking of enablement for an undefined perturbation of an undefined biological pathway. The Examiner contends that the specification, while being enabling for perturbing biological pathways wherein at least one reasonably is affected by a drug action, does not reasonably provide enablement for any undefined perturbation of an undefined biological pathway. Applicants have amended the claims to more particularly point out that in the computer systems of the invention, the one or more biological pathway responses that are combined to form, e.g., a model drug response, *comprise at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in the cell type.* The rejections over claims 41-45, 48-56 and 58-87 under 35 U.S.C. § 112, first paragraph, are therefore obviated, and should be withdrawn.

Claims 41-45 and 48-87 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that claim 45 recites the "Levenberg-Marquandt method" but that this is not cited anywhere in the specification as filed. As discussed above, the Levenberg-Marquandt method is described and referenced in the specification at page 46, lines 11-28. The rejection of claim 45 under 35 U.S.C. § 112, second paragraph, is therefore in error, and should be withdrawn.

The Examiner also contends that claims 41 and 80-87, and claims dependent thereon, require that at least three biological pathway responses are evaluated and that there is at least one biological pathway which has less than the "best" scaling transformation. Applicants respectfully submit that the Examiner's contention is based on an erroneous understanding as to what the "best" scaling transformation refers to. The computer systems of the invention determine best scaling transformations for *each and every* biological pathway of the one or more biological pathways so that the function of the difference between, e.g., the drug response and the model drug response, is minimized. Thus, a "best" scaling transformation refers to a transformation that minimizes the function of difference between, e.g., the drug

response and the model drug response as compared to other scaling transformations of the *same* biological pathway that do not minimize the function. Applicants direct the attention of the Examiner to the specification at page 45, lines 20-31, where a description of this subject matter is given, and to, for example, part (c) of claim 41, which recites that each of the one or more biological pathway responses that combine to form the model drug response are subject to an independent scaling transformation. The rejection of claims 41 and 80-87, and claims dependent thereon, under 35 U.S.C. § 112, second paragraph, is therefore in error, and should be withdrawn.

The Examiner further contends that the phrase "one or more biological pathway responses" is unclear because the phrase contains a conflict between "one" and "responses." Applicants respectfully point out that the phrase is a commonly accepted and understood usage in the English language, meaning "one biological pathway response or two or more biological pathway responses." The phrase has also seen wide use in claim language (see, e.g., examples given on pages O-6 and O-7 of the Attorney's Dictionary of Patent Claims, Irwin M. Aisenberg, Lexis Publishing, 2000; copies of which are attached herewith as Exhibit E). Applicants respectfully submit that the skilled artisan having read the specification would be able to understand its meaning. The rejection of the phrase "one or more biological pathway responses" under 35 U.S.C. § 112, second paragraph, is therefore in error, and should be withdrawn.

THE OBJECTION TO THE DISCLOSURE SHOULD BE WITHDRAWN

The disclosure is objected to because of an informality in the specification. The Examiner contends that on page 49, line 29 the word "date" appears to be a misspelling of "data." Applicants have amended the specification to correct the typographical error. The objection is therefore obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection

or objection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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By Geraldine Lee Bard 32,605

Date November 19, 2001

Adriane M. Antler (Reg. No.)

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Enclosures

EXHIBIT A: MARKED VERSION OF AMENDED PARAGRAPHS IN THE SPECIFICATION
U.S. APPLICATION SERIAL NO. 09/374,565
(ATTORNEY DOCKET NO. 9301-058)

(as amended November 19, 2001)

On page 49, please amend the paragraph beginning "According to the preferred method", as follows:

According to the preferred method, a residual distribution is constructed by repetitively solving Eqn. 5 with randomized input data and accumulating the residuals to form the empirical residual distribution. Thereby, the constructed empirical residual distribution arises from random data that has the same population statistics as the actual data. In detail, first, either the drug response [date] <u>data</u> or the pathway response data (but not both) are randomized in step 505 with respect to the drug exposure levels or the perturbation control parameters, respectively. This randomization transformation is represented by the following transformation.

$$\begin{aligned} D_k(t_l) &\leftarrow D_k(t_{\Pi(l)}) \\ R_{i,k}(p_{i,l}) &\leftarrow R_{i,k}(p_{i,\Pi(l)}) \end{aligned} \qquad \textbf{(10)}$$

In Eqn. 10, Π represents a perturbation independently chosen for each cellular constituent. Either the drug response or the each pathway response (but not both) is randomized according to Eqn. 10. Accordingly, the randomized drug or pathway response data are derived from the measured data by independent perturbations of the measurement points. Second, Eqn. 5 is then solved by the chosen numerical approximation technique in step 504 and the value of the resulting residual saved. These steps are repeated for enough randomizations to construct a sufficiently significant expected probability distribution of residuals. In order to obtain confidence levels of 99% or better (*i.e.*, a P-value less than 0.01), then more than 100 randomizations are needed.

EXHIBIT B: CLEAN VERSION OF AMENDED PARAGRAPHS IN THE SPECIFICATION
U.S. APPLICATION SERIAL NO. 09/374,565
(ATTORNEY DOCKET NO. 9301-058)

(as amended November 19, 2001)

On page 49, please replace the paragraph beginning "According to the preferred method" with the following paragraph:

According to the preferred method, a residual distribution is constructed by repetitively solving Eqn. 5 with randomized input data and accumulating the residuals to form the empirical residual distribution. Thereby, the constructed empirical residual distribution arises from random data that has the same population statistics as the actual data. In detail, first, either the drug response data or the pathway response data (but not both) are randomized in step 505 with respect to the drug exposure levels or the perturbation control parameters, respectively. This randomization transformation is represented by the following transformation.

$$\begin{aligned} D_k(t_l) &\leftarrow D_k(t_{\Pi(l)}) \\ R_{i,k}(p_{i,l}) &\leftarrow R_{i,k}(p_{i,\Pi(l)}) \end{aligned} \qquad \textbf{(10)}$$

In Eqn. 10, Π represents a perturbation independently chosen for each cellular constituent. Either the drug response or the each pathway response (but not both) is randomized according to Eqn. 10. Accordingly, the randomized drug or pathway response data are derived from the measured data by independent perturbations of the measurement points. Second, Eqn. 5 is then solved by the chosen numerical approximation technique in step 504 and the value of the resulting residual saved. These steps are repeated for enough randomizations to construct a sufficiently significant expected probability distribution of residuals. In order to obtain confidence levels of 99% or better (*i.e.*, a P-value less than 0.01), then more than 100 randomizations are needed.

EXHIBIT C: MARKED VERSION OF AMENDED CLAIMS
U.S. APPLICATION SERIAL NO. 09/374,565
(ATTORNEY DOCKET NO. 9301-058)

(as amended November 19, 2001)

41. (Three Times Amended) A computer system for [identifying] determining biological pathways involved in the action of a drug in a cell type, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of:

(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

49. (Twice Amended) The computer system of claim 48 wherein the expected probability distribution of minimized determined values of said function is determined by:

(i) randomizing the drug response with respect to the plurality of levels of drug exposure [and] or randomizing the model drug response by randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;

(ii) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the [randomized] drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or

determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and

(iii) [minimizing said determined theoretical value of the function by varying the scaling transformations of the one or more randomized biological pathway responses to obtain scaling transformations that minimize said determined theoretical value of the function; and

(iv)] repeating steps (i) through [(iii)] (ii) to determine a plurality of theoretical minimum values,

wherein said plurality of minimum values forms said expected probability distribution of minimized values.

80. (Twice Amended) A computer system for identifying a more pathway specific drug candidate than an initial drug candidate comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) [identifying] determining the biological pathways involved in the action of an initial drug candidate by a method comprising:

(i) receiving an initial drug response of said initial drug candidate in a cell of a cell type, said initial drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the initial drug candidate,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said initial drug candidate in said cell type,

(iii) forming a model initial drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said initial drug response and said model initial drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the initial drug candidate;

(b) [identifying] determining the biological pathways involved in the action of a modified drug candidate, said modified drug candidate having a modified structure of the initial drug candidate, by a method comprising:

(i) receiving a modified drug response of said modified drug candidate in a cell of the cell type, said modified drug response comprising quantitative measurements of a plurality of cellular constituents in a

cell of the cell type at a plurality of levels of exposure to the modified drug candidate,

(ii) forming a model modified drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said modified drug response and said model modified drug response, and

(iv) minimizing the determined value of the function of the difference between said modified drug response and said model modified drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate, and

wherein said modified drug candidate is identified as a more pathway-specific drug candidate than said initial drug candidate if fewer biological pathways are [identified] involved in the action of said modified drug candidate than in the action of said initial drug candidate.

81. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in the action of a drug and that mediate side-effects of the drug, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) [identifying] determining the biological pathways involved in the action of a first drug by a method comprising:

(i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,

(iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said first drug response and said model first drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

(b) [identifying] determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:

(i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,

(ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said second drug response and said model second drug response, and

(iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the [modified] <u>second</u> drug [candidate]; and

(c) identifying specific biological pathways involved in the action of the first drug that are different from those biological response pathways involved in the action of the second drug so that one or more specific biological pathways that are involved in the action of the first drug and that mediate side-effects of the first drug are identified.

82. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in mediating therapeutic efficacy for a disease or disorder, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) [identifying] <u>determining</u> the biological pathways involved in the action of a first drug by a method comprising:

(i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the [fist] first drug,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,

(iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said first drug response and said model first drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

(b) [identifying] determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:

(i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,

(ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said second drug response and said model second drug response, and

(iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the [modified] second drug [candidate]; and

(c) identifying specific biological pathways involved in the action of both the first and second drugs so that one or more specific biological pathways that are involved in the action of said first drug and mediate therapeutic efficacy for the disease or disorder are identified.

83. (Twice Amended) A computer system for [identifying] determining biological pathways involved in the action of a drug in a cell type comprising

a process, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of a function of the difference between a provided drug response and a model drug response, wherein:

(a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of

perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(b) said provided drug response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said drug; and

(c) said model drug response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations [identifies] represents the biological pathways involved in the action of said drug in said cell type.

85. (Twice Amended) The computer system of claim 84 wherein the expected probability distribution is obtained by a method comprising:

(a) randomizing the drug response with respect to the plurality of levels of drug exposure, or, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;

(b) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or [a theoretical minimum value of the function by] determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and

(c) repeating steps (a) through (b), so that a plurality of theoretical minimum values is thereby determined,

wherein the plurality of theoretical minimum values forms the expected probability distribution.

86. (Twice Amended) A computer system for [identifying] determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of an objective function of the difference between a received environmental response and a model environmental response, wherein:

(a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;

(b) said received environmental response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said environmental change; and

(c) said model environmental response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations [identifies] represents the biological pathways involved in the effect of said environmental change upon said cell type.

87. (Twice Amended) A computer system for [identifying] determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) receiving an environmental response to said environmental change upon said cell type, said environmental response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of exposure to said environmental change;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;

(c) forming a model environmental response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said environmental response and said model environmental response; and

(e) minimizing said determined value of said function by varying the scaling transformation of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations [identifies] represents the biological pathways involved in the effect of said environmental change upon said cell type.

Claim 88 has been added.

EXHIBIT D: CLEAN VERSION OF PENDING CLAIMS
U.S. APPLICATION SERIAL NO. 09/374,565
(ATTORNEY DOCKET NO. 9301-058)

(as amended November 19, 2001)

41. (Three Times Amended) A computer system for determining biological pathways involved in the action of a drug in a cell type, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of:

(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

42. (Amended) The computer system of claim 41 wherein said steps of receiving comprise making said drug response and said biological pathway responses available in said memory.

43. The computer system of claim 41 wherein said forming a model drug response comprises adding said one or more biological pathway responses.

44. (Amended) The computer system of claim 41 wherein said function comprises a sum of squares of the differences of said drug response and said model drug response at said levels of drug exposure, said model drug response being provided at said levels of drug exposure by transforming by said scaling transformations said levels of drug exposure to corresponding levels of perturbations to each of said biological pathways and by interpolating said biological pathway responses to said corresponding levels of perturbations.

45. The computer system of claim 41 wherein said minimizing comprises performing the Levenberg-Marquandt method.

48. (Amended) The computer system of claim 41 wherein the method performed by said processor further comprises the steps of:

(f) determining an expected probability distribution of minimized determined values of said function, and

(g) assessing the statistical significance of the minimized determined value of said function in view of the expected probability distribution of minimized determined values of said function.

49. (Twice Amended) The computer system of claim 48 wherein the expected probability distribution of minimized determined values of said function is determined by:

(i) randomizing the drug response with respect to the plurality of levels of drug exposure or randomizing the model drug response by randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;

(ii) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model

drug response, if the one or more biological pathway responses are randomized, or

determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and

(iii) repeating steps (i) through (ii) to determine a plurality of theoretical minimum values,

wherein said plurality of minimum values forms said expected probability distribution of minimized values.

50. (Amended) The computer system of claim 41 wherein the method performed by the processor further comprises a step of verifying that said biological pathways are biological pathways involved in the action of said drug in said cell type by a method comprising selecting a model response that behaves most similarly to a combined drug-perturbation response, said combined drug perturbation response being provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of said cell type exposed simultaneously to one or more levels of said exposure to said drug and to one or more levels of perturbations in said one or more biological pathways,

wherein the model drug response is selected from the group consisting of:

(i) a first model drug response comprising the combination of one or more biological pathway responses subject to the best scaling transformations evaluated at one or more first sums, each first sum being the sum of one of said one or more levels of drug exposure subject to said scaling transformations and one of said one or more levels of perturbations to said biological pathways.

(ii) a second model drug response comprising one or more second sums, each second sum being the sum of said drug response evaluated at one of said one or more levels of drug exposure and said combination of said one or more biological pathway responses subject to the best scaling transformations evaluated at one of said one or more levels of perturbations to said biological pathways,

wherein said biological pathways are verified as biological pathways actually involved in the action of said drug in said cell type if the first model response is selected.

51. The computer system of claim 41 wherein the method performed by the processor further comprises a step of assigning a cellular constituent present in said drug response to the one of said one or more biological pathways in which the biological pathway response of the cellular constituent subject to its best scaling transformation has the greatest correlation with the drug response of the cellular constituent.

52. The computer system of claim 41 wherein said scaling transformations comprise transformations of said levels of drug exposure to corresponding levels of said perturbations to said biological pathways.

53. The computer system of claim 52 wherein said transformations of said levels of drug exposure are by linear mapping.

54. (Amended) The computer system of claim 41 wherein said one or more programs further cause said processor to interpolate the quantitative measurements of cellular constituents of the biological pathway in said cell of said cell type at a plurality of levels of perturbation so that the one or more biological pathway responses are interpolated.

55. The computer system of claim 54 wherein the interpolating comprises approximation by a sum of spline functions.

56. The computer system of claim 54 wherein the interpolating comprises approximation by a Hill function.

57. The computer system of claim 41 wherein the one or more biological pathways in the cell type are those biological pathways likely to be involved in the action of the drug in the cell type.

58. The computer system of claim 41 wherein the one or more biological pathways are selected from a compendium of biological pathways present in the cell type.

59. The computer system of claim 41 wherein the cell type is substantially isogeneic to Saccharomyces cerevisiae.

60. The computer system of claim 41 wherein the cellular constituents comprise abundances of a plurality of RNA species present in the cell type.

61. (Amended) The computer system of claim 60 wherein the abundances of the plurality of RNA species are measured by a method comprising contacting a gene transcript array with RNA from a cell of the cell type, or with cDNA derived therefrom, wherein a gene transcript array comprises a surface with attached nucleic acids or nucleic acid mimics, said nucleic acids or nucleic acid mimics being capable of hybridizing with said plurality of RNA species or with cDNA species derived therefrom.

62. (Amended) The computer system of claim 61 wherein the quantitative measurements of cellular constituents in step (a) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is exposed to said drug, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said drug, and

wherein said quantitative measurements of cellular constituents in step (b) are provided by a method comprising contacting one or more gene transcript arrays (i) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is exposed to said perturbation to said biological pathway, and (ii) with RNA, or with cDNA derived therefrom, from a cell of said cell type that is not exposed to said perturbation to said biological pathway.

63. The computer system of claim 41 wherein the cellular constituents comprise abundances of a plurality of protein species present in the cell type.

64. The computer system of claim 63 wherein the abundances of the plurality of protein species are measured by a method comprising contacting an antibody array with proteins from a cell of the cell type,

wherein the antibody array comprises a surface with attached antibodies that are capable of binding with the plurality of protein species.

65. The computer system of claim 63 wherein the abundances of the plurality of protein species are measured by a method comprising performing two-dimensional electrophoresis of proteins from a cell of the cell type.

66. The computer system of claim 41 wherein the cellular constituent comprise activities of a plurality of protein species present in the cell type.

67. The computer system of claim 41 wherein the one or more biological pathways in the cell type comprise biological pathways originating at one or more specific cellular constituents, and wherein the perturbations to the biological pathways are performed by a method comprising modifying the one or more specific cellular constituents.

68. The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising causing expression of the one or more specific cellular constituents under the control of a controllable expression system.

69. (Amended) The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllable transfection of genes expressing the one or more specific cellular constituents.

70. The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing abundances of RNA species encoding the one or more specific cellular constituents in a cell of the cell type.

71. The computer system of claim 70 wherein the method of controllable decreasing abundances of RNA species comprises exposing a cell of the cell type to ribozymes targeted to cleave the RNA species.

72. The computer system of claim 67 wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the rate of translation of RNA species encoding the one or more specific cellular constituents in a cell of the cell type.

73. The computer system of claim 72 wherein the method of controllably decreasing the rate of translation of RNA species comprises exposing a cell of the cell type to antisense nucleic acids or antisense nucleic acid mimics that hybridize to the RNA species or to DNA encoding the RNA species.

74. (Amended) The computer system of claim 67 wherein the one or more specific cellular constituents are abundances of protein species or activities of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the abundances in a cell of the cell type.

75. The computer system of claim 74 wherein the method of controllably decreasing the abundances comprises causing expression in a cell of the cell type of the one or more protein species as fusion proteins comprising the protein species and a degron, wherein the degron is controllable to increase the rate of degradation of the protein species.

77.(Amended) The computer system of claim 67 wherein the one or more specific cellular constituents are activities of protein species, and wherein the one or more specific cellular constituents are modified by a method comprising controllably decreasing the activities in a cell of the cell type.

78. (Amended) The computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to drugs which directly and specifically inhibit the activities of the protein species.

79. (Amended) The computer system of claim 77 wherein the method of controllably decreasing the activities comprises exposing a cell of the cell type to dominant negative mutant protein species, wherein the dominant negative mutant protein species are proteins inhibiting said activities.

80. (Twice Amended) A computer system for identifying a more pathway specific drug candidate than an initial drug candidate comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) determining the biological pathways involved in the action of an initial drug candidate by a method comprising:

(i) receiving an initial drug response of said initial drug candidate in a cell of a cell type, said initial drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the initial drug candidate,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said initial drug candidate in said cell type,

(iii) forming a model initial drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said initial drug response and said model initial drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the initial drug candidate;

(b) determining the biological pathways involved in the action of a modified drug candidate, said modified drug candidate having a modified structure of the initial drug candidate, by a method comprising:

(i) receiving a modified drug response of said modified drug candidate in a cell of the cell type, said modified drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the modified drug candidate,

(ii) forming a model modified drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said modified drug response and said model modified drug response, and

(iv) minimizing the determined value of the function of the difference between said modified drug response and said model modified drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the modified drug candidate, and

wherein said modified drug candidate is identified as a more pathway-specific drug candidate than said initial drug candidate if fewer biological pathways are involved in the action of said modified drug candidate than in the action of said initial drug candidate.

81. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in the action of a drug and that mediate side-effects of the drug, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) determining the biological pathways involved in the action of a first drug by a method comprising:

(i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,

(iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said first drug response and said model first drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first

combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

(b) determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:

(i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,

(ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said second drug response and said model second drug response, and

(iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the second drug; and

(c) identifying specific biological pathways involved in the action of the first drug that are different from those biological response pathways involved in the action of the second drug so that one or more specific biological pathways that

are involved in the action of the first drug and that mediate side-effects of the first drug are identified.

82. (Twice Amended) A computer system for identifying one or more specific biological pathways that are involved in mediating therapeutic efficacy for a disease or disorder, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) determining the biological pathways involved in the action of a first drug by a method comprising:

(i) receiving a first drug response of said first drug in a cell of a cell type, said first drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the first drug,

(ii) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of the cell type at a plurality of levels of perturbation to the biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said first drug in said cell type,

(iii) forming a model first drug response as a first combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said first combination is subject to an independent scaling transformation,

(iv) determining the value of a function of the difference between said first drug response and said model first drug response, and

(v) minimizing the determined value of the function by varying the scaling transformation of said one or more biological pathways in the first

combination to obtain a first set of best scaling transformations that minimize the determined value of the function,

so that the first combination of said one or more biological responses subject to the first set of best scaling transformation represents the biological response pathways involved in the action of the first drug;

(b) determining the biological pathways involved in the action of a second drug, wherein said second drug is different from said first drug and exhibits therapeutic efficacy for the same disease or disorder as said first drug, by a method comprising:

(i) receiving a second drug response of said second drug in a cell of the cell type, said second drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to the second drug,

(ii) forming a model second drug response as a second combination of the one or more biological pathway responses, wherein each of said one or more biological pathway responses in said second combination is subject to an independent scaling transformation,

(iii) determining the value of a function of the difference between said second drug response and said model second drug response, and

(iv) minimizing the determined value of the function of the difference between said second drug response and said model second drug response by varying the scaling transformation of said one or more biological pathways in the second combination to obtain a second set of best scaling transformations that minimize the determined value of the function,

so that the second combination of said one or more biological responses subject to the second set of best scaling transformation represents the biological response pathways involved in the action of the second drug; and

(c) identifying specific biological pathways involved in the action of both the first and second drugs so that one or more specific biological pathways that are involved in the action of said first drug and mediate therapeutic efficacy for the disease or disorder are identified.

83. (Twice Amended) A computer system for determining biological pathways involved in the action of a drug in a cell type comprising

a process, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of a function of the difference between a provided drug response and a model drug response, wherein:

(a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in action of said drug in said cell type;

(b) said provided drug response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said drug; and

(c) said model drug response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the action of said drug in said cell type.

84. (Amended) The computer system of claim 83 wherein said computer system assigns a statistical significance to the combination of said one or more biological pathway responses subject to said best scaling transformations, wherein the statistical significance is assigned by a method comprising:

(a) obtaining an expected probability distribution of minimized values of the function; and

(b) assessing statistical significance of an actual minimized value of the function in view of the expected probability distribution, wherein the actual minimized value of the function is determined from the provided drug response and the model drug response.

85. (Twice Amended) The computer system of claim 84 wherein the expected probability distribution is obtained by a method comprising:

(a) randomizing the drug response with respect to the plurality of levels of drug exposure, or, randomizing the model drug response by a method comprising randomizing the one or more biological pathway responses with respect to the plurality of levels of perturbation to the one or more biological pathways;

(b) determining a theoretical minimum value of the function by a method comprising:

determining best scaling transformations of the one or more randomized biological pathway responses which minimize the function of the difference between the drug response and the randomized model drug response, if the one or more biological pathway responses are randomized, or

determining best scaling transformations of the one or more biological pathway responses which minimize the function of the difference between the randomized drug response and the model drug response, if the drug response is randomized; and

(c) repeating steps (a) through (b), so that a plurality of theoretical minimum values is thereby determined,

wherein the plurality of theoretical minimum values forms the expected probability distribution.

86. (Twice Amended) A computer system for determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method that comprises determining the best scaling transformation of one or more biological pathway responses which minimize the value of an objective function of the difference between a received environmental response and a model environmental response, wherein:

(a) said one or more biological pathway responses are the product of a method comprising quantitatively measuring cellular constituents of one or more biological pathways in a cell of said cell type at a plurality of levels of perturbation to said biological pathways, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;

(b) said received environmental response is provided by a method comprising quantitatively measuring a plurality of cellular constituents in a cell of the cell type at a plurality of levels of exposure to said environmental change; and

(c) said model environmental response is represented as a combination of said one or more biological pathway responses, each of said one or more biological pathway responses in said combination being subject to an independent scaling transformation; and

wherein the combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the effect of said environmental change upon said cell type.

87. (Twice Amended) A computer system for determining biological pathways involved in the effect of an environmental change upon a cell type, said computer system comprising:

a processor, and

a memory coupled to said processor and encoding one or more programs,

wherein said one or more programs cause said processor to perform a method comprising the steps of:

(a) receiving an environmental response to said environmental change upon said cell type, said environmental response comprising quantitative measurements

of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of exposure to said environmental change;

(b) receiving one or more biological pathway responses, each of said one or more biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to said biological pathway, said one or more biological pathway responses comprising at least one biological pathway response from a biological pathway that is likely to be involved in effect of said environmental change on said cell;

(c) forming a model environmental response as a combination of said one or more biological pathway responses, wherein each of said one or more biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said environmental response and said model environmental response; and

(e) minimizing said determined value of said function by varying the scaling transformation of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents the biological pathways involved in the effect of said environmental change upon said cell type.

88. (New) A computer system for representing measured drug response data of a drug in a cell type, said computer system comprising a processor and a memory coupled to said processor, said memory encoding one or more programs, said one or more programs causing said processor to perform a method comprising the steps of:

(a) receiving a drug response of said drug in said cell type, said drug response comprising quantitative measurements of a plurality of cellular constituents in a cell of said cell type at a plurality of levels of drug exposure;

(b) receiving a plurality of biological pathway responses, each of said plurality of biological pathway responses comprising quantitative measurements of cellular constituents of a biological pathway in a cell of said cell type at a plurality of levels of a perturbation to

said biological pathway, said plurality of biological pathway responses comprising biological pathway responses sufficient to cover all pathways likely to be involved in action of said drug in said cell type;

(c) forming a model drug response as a combination of said plurality of biological pathway responses, wherein each of said plurality of biological pathway responses in said combination is subject to an independent scaling transformation;

(d) determining the value of a function of the difference between said drug response and said model drug response; and

(e) minimizing said determined value of said function by varying the scaling transformations of said one or more biological pathway responses to obtain best scaling transformations that minimize said determined value of said function;

wherein said combination of said one or more biological pathway responses subject to said best scaling transformations represents said measured drug response data of said drug in said cell type.